The Rationality or Irrationality of Ganglion Blocking Agents in Hypertension

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INTRODUCTION

I have regarded this title, a most provocative one, as an invitation to the higher speculation, and will simply set out my own thoughts as clearly as I have been able to formulate them, in the hope that they may at least bring out into the open some of the unspoken assumptions in the use of ganglion block.

A laboratory worker is, of course, hampered straight away by the realization that there seems no agreement on a rational etiology of hypertension. Obviously, unless one knows the cause of a disease, it is difficult to discuss its treatment in any but empirical terms. But, for hypertension, there seems to be no specific account of pathogenesis so convincing as to command general assent. In a sense, there are too many possible explanations; and many shrewd clinicians noticeably refrain from chancing their arm as to which explanation it is that they really back. The main concepts are, perhaps, the following: (1) Hypertension is neurogenic in origin, in the sense that in the hypertensive patient, the prime mover is an abnormal activity of his autonomic nervous system, leading to a sustained sympathetic tone and rise in blood pressure. (2) The increased peripheral resistance is due, not to nervous influences, but to a circulating vasoconstrictor substance. Most plausibly, this is a factor originating from changes in the kidney, less plausibly a sympathetic amine. (3) The abnormality is in neither of these directions, but in the blood vessels themselves, so that they respond to ordinary influences, whether nervous or hormonal, by an exaggerated contraction; or the responsiveness of their muscle is not specially modified, but their structure is such that their lumens at normal muscle tone are smaller than usual. (4) It seems to be implied in some treatments that the fundamental defect is connected primarily with the adrenal cortex, and that the ensuing changes in electrolyte and fluid distribution result in hypertension. There are, of course, other suggestions. But these four seem pretty representative, in placing the lesion respectively in the nervous system, in circulating hormones, in the vessels themselves or in the control of the volume of blood perfusing them. I have taken it as my duty, being interested in ganglion block, to select the first as being *the* cause of hypertension; I propose, therefore, to argue this case, and further, that so far as the other explanations are true, it is because they are sequels to hypertension of nervous origin. The material of the argument, of course, is those patients who begin symptomless and with no detectable pathology save the sign of a raised blood pressure, and of

whom a small proportion proceed to the characteristic and distressing picture termed malignant hypertension.

ARGUMENTS FOR THE NEUROGENIC HYPOTHESIS

I can see four arguments in favor of hypertension being primarily due to an overactivity of the autonomic nervous system. They are, of course, also justifications for the use of ganglion block.

1. The first, which can be called briefly the *geographical argument,* may be put thus. In the early days of hexamethonium, one objection was sometimes raised to its use: that the raised blood pressure in hypertension is a valuable protective response, preserving a satisfactory blood flow to the organs in which a narrowing of arterioles had occurred. This implied that to lower the blood pressure might deprive vital organs of their necessary blood flow. It seems to me quite correct to predict that lowering the blood pressure *per se* could well be harmful—except under one circumstance: this is, if the reduction in blood pressure was achieved by means which dilated those very vessels which were constricted by the hypertensive process. Clearly it would be no use, for instance, to vasodilate muscle blood vessels selectively, if the vasoconstrictive process also affected viscera, skin, heart, brain, suprarenals, and so on. Equally, one would not expect successful therapy from a general vasodilatation, if the pathologic vasoconstriction was spatially limited. But if the geography, so to speak, of the vasodilatation on which the blood pressure fall depended was the same as the geography of the vasoconstriction on which the hypertension depended, blood flows would be little altered, and the benefit of a smaller hydrostatic pressure in the arterioles would be gained. One could infer, then, from the fact that ganglion blocking agents are so effective, that the nature of the vasoconstrictive process which gives rise to hypertension has the same distribution as the vasodilation produced by ganglion block. Since the distribution of ganglion block is necessarily that of the autonomic nervous system, one then has an argument that the distribution of the vasoconstrictor process in hypertension is also that of the sympathetic autonomic nervous system.

It could be objected, however, that almost *any* method of lowering the blood pressure is also effective in hypertension. But it is interesting how many of the effective attacks are, like ganglion block, through the autonomic. Sympathectomy, Veratrum alkaloids (whose important action seems to be the relief of sympathetic tone), central depressants, reserpine (attacking centrally, and also more specifically the adrenergic nerves) all have this in common. It is, perhaps, significant that nitrites have not been very successful, nor lowering the blood pressure by arteriovenous fistula. A more searching objection would be to say that paralysis of the sympathetic outflow will have such a diffuse action that *any* diffuse vasoconstriction should be countered by it. Nevertheless, the fact that our modern treatment of hypertension focuses, anatomically, so much on the autonomic justifies a special interest in autonomic causes for the disease.

2. The second argument for a nervous cause starts with the premise that if the blood pressure rises from any of the other causes, one would anticipate that the neurogenic tone in the patient would be reduced by the normal operation of the buffer nerves. The scope of action of an autonomic blocking agent should be much smaller than in the normal individual. But of course

the practical result is the reverse; a normal individual, supine, shows usually a trivial fall in blood pressure, whereas a supine hypertensive exhibits a substantial one. Therefore, neurogenic tone is increased, not decreased, in hypertension, and the other causes do not operate. A good deal depends here on the validity of the premise. It is easily verified in one way; thus, if one infuses a peripheral vasoconstrictor into an animal so as to raise the blood pressure, ganglion blocking agents now have rather a small depressor action. On the other hand, if one raises the blood pressure by some method involving an increase in autonomic tone, such as asphyxia or by establishing a rather light plane of anesthesia, then ganglion blocking agents can be extraordinarily effective.

However, it may be objected that this type of test is too acute. Green, McCubbin and Page produced evidence that if a *sustained* humoral hypertension was achieved in dogs, then the buffer nerve afferent discharge, initially very vigorous, steadily fell away, as though this sensory area became accommodated to its new situation. From this experiment, one would suppose that the autonomic efferent discharge in the hypertensive could return to a state comparable to that seen in a normal individual even if the hypertension was humoral. However, we are still left with the difficulty of explaining, with this sort of model, why ganglion blocking agents work *better* in the hypertensive than in the normal. Even if there is some degree of autonomic activity, one could not predict that when it is removed, in the presence of a strong humoral vasoconstriction, any substantial fall of blood pressure would necessarily occur, any more than one would expect that if two strong men are holding up a weight and one lets go, the other one will necessarily let it fall. I would like to suggest that, in fact, the natural history of hypertension provides us with a model experiment. Some cases begin fully sensitive to autonomic block and then develop a fixed high blood pressure, progressively resistant to block and accompanied by such signs of arteriolar damage that one is willing to suppose that renal humoral factors have taken control. The fixity of the blood pressure at this stage underlines the significance of its lability at an earlier phase.

A second objection can also be raised: that the large fall of blood pressure produced by ganglion block in many hypertensives is due, not to an increased autonomic nervous discharge from the C.N.S., but to an increased reaction by the blood vessels to a normal discharge. To support this notion, some workers (though not all) report an increased response to vasoconstrictor drugs in hypertensives, compared to normal. Perhaps one should wait until this is established. But two comments can be made. First, it does not lessen the importance of neurogenic tone, since it implies that, given a small backing of some hormonal vasoconstrictor, neurogenic influences become far more important than they might be believed to be from tests on normal individuals. As neurogenicity is expelled at one door it comes back with renewed force at another! Second, if a given quantum of nervous activity yields a bigger effector response than normally, one would expect homeostatic mechanisms to check this response by reducing the intensity of the nervous discharge, so keeping blood pressure near its proper level. The argument of exaggerated vessel reactivity may explain some of the facts, but, by itself, cannot explain the most important one, the hypertension itself.

3. The third argument bases itself on the relative commonness of hypertension and on the evidence provided by Pickering and his colleagues, and

by others, that blood pressure is a unimodally distributed quantity: that, in other words, hypertensives are the right-hand tail of a distribution curve. This means that, for its pathogenesis, we must look for a cause which is both common and an extension of normal processes. What common, normal hypertensions are there? As far as I know, those mediated by the autonomic in so-called "stressful" situations are the only examples one can quote. If our everyday life is made up of fluctuations in blood pressure in response to circumstance, it seems perfectly reasonable to suppose that sometimes these fluctuations may become more prolonged and more persistent than usual. To look further for a *primary* cause of hypertension seems rather like trying to explain the popularity of pin-up girls, not by the attractiveness of the girls portrayed, but on a theory, say, that young men like hammering tacks into walls!

4. The fourth argument one can advance is that the whole picture of hypertension is interpretable by taking a neurogenic starting-point. By this I mean that if one postulates an initial autonomic activity, one can then readily suppose that in due course the blood vessels, through their exposure to a higher hydrostatic pressure through the years, will change in their structure and diameter; that this autonomic activity could be associated with an excitation of the adrenal cortex, perhaps mediated via adrenalin secretion and the anterior pituitary, leading to those evidences of sodium retention and aldosteronism which have been put forward; and that in the course of time, as arteriolar damage becomes worse, renal damage may follow in turn to produce a supplementing and finally dominant renal hypertension. This is a picture which, speculative though it is, I believe many people take as a working model. Its attraction seems to be simply that it provides a sequential analysis of hypertension, which does not seem to flow so plausibly from the other approaches. I do not know, for instance, of any satisfactory physiologic evidence that an adrenocortical overactivity could commonly give rise to a physiologic state which could be interpreted as autonomic overactivity, although, as just mentioned, one can envisage a state in which autonomic overactivity could give rise to adrenocortical activity.

One can therefore, propose that the prime cause of hypertension is a sympathetic overactivity, and that the features of its later development have been elicited by this initial neurogenic excitation.

SOME OBJECTIONS

There are, however, still some objections to meet. The first bears almost directly on pharmacology. If you give a ganglion blocking agent to a hypertensive, it seems that the blood pressure only rarely falls to the same level observed for a normotensive. This provides the basis for the allotment of the excess of blood pressure over the normal into a neurogenic and non-neurogenic fraction. I am not sure, however, that this necessarily holds, because of the difficulty in producing complete ganglion block. One must remember, for instance, that it is usually impossible to produce in an animal, with any dose of ganglion blocking agent, a blood pressure as low as that achieved by anesthesia or destruction of the spinal cord. My own guess, which I have argued elsewhere, is that the accessory ganglia, those cells located, not in the pre- and paravertebral ganglion chains, but in the rami

or in spinal nerves, are as resistant to drugs as they are elusive to the surgeon's scalpel; and that this resistance is a result of their still being cloaked by an extension into peripheral nerve of the blood-brain barrier. In apportioning the division between neurogenic and non-neurogenic, it is not enough simply to record the lowest blood pressure obtained with a large dose of blocking agent; it is also necessary to prove that *all* vasomotor responses have been obliterated. If they have not been, there may well be an additional neurogenic fraction of pressure still present. Clearly, if the pressure floor rises, as observations continue in a deteriorating patient, one could attribute the increment to non-neurogenic factors. But the initial apportionment offers considerable difficulties, and a relatively high floor, in a first test, cannot be directly attributed to, say, humoral influences.

A second objection arises from the known association of rising blood pressure with increasing age. It is difficult, even for a fervent speculator, to assume that autonomic activity will increase not only up to the prime of life but beyond it, even to the age of the lean and slippered pantaloon; especially when the structural changes in the arteries which age brings are so obvious. It could be argued, however, that the rise with age represents, not a primary degeneration of the blood vessels, but the result of a lifetime of autonomic activity, that every autonomic adventure leaves its debris on the sands of cardiovascular time. One can note, too, that it is estimated that age constitutes only about one-fifth of the total sources of variation which determine blood pressure. Nevertheless, one should probably admit that with advancing age, the rising normal blood pressure provides a steadily higher baseline from which other pressor processes will start. The other aspect of this study, demonstrating a multifactorial inheritance of blood pressure level, is not, of course, indicative of any particular pathogenesis. It was around 50 years ago that Francis Galton, in his fascinating book *Hereditary Genius*, showed that qualities like scientific, military or political ability, even the stringent demands of ecclesiastical distinction and piety, were inherited. If these complicated faculties can be passed on by the genes, variations in the humbler autonomic function should not be beyond their capacity.

The last objection to the neurogenic hypothesis is, perhaps, that the evidence for it is so largely circumstantial. To a large extent it rests on, so to speak, the method of subtraction—that is, by comparing the physiologic state of a subject before and after some measure of autonomic attack, and attributing the difference to autonomic factors. But we have seen some of the difficulties of the method, particularly on the quantitative side. Can more direct evidence be obtained? The prospect does not look very hopeful. For one cannot record action potentials directly in human autonomic nerve pathways. Nor does it seem that we can identify sympathetic activity by noradrenalin release. The noradrenalin excretion of hypertensives (apart from pheochrome tumors) is hardly different from normal. This might be taken as evidence against a neurogenic hypothesis. But we know that, of an infused quantity of noradrenalin, only around 3 per cent appears in the urine; the fraction that would be excreted of that released at sympathetic nerve endings could only be minute, when it has been exposed to destruction at the site of release and to dispersion throughout the body. On the background of normal catechol amine output, any output from this cause could well be undetectable.

One may conclude, then, that the neurogenic hypothesis, as prime mover of the hypertensive process, can be held, resting for its support on the arguments (1) that an autonomic attack is successful; (2) that the evidence for enhanced autonomic tone is incompatible with other theories; (3) that it invokes as the cause for a condition which is common and an extension of normality a mechanism which is common and normal; and (4) that it allows a satisfactory sequential analysis of the natural history of the disease.

One may feel, however, that this sort of discussion is so undecisive as to be unprofitable. Perhaps this is true. Perhaps, on the other hand, a concentrated attention on the autonomic aspects of hypertension, rather than on other aspects or on hypotensive drugs in general, might be rewarding. One point that arises, for instance, is the need for thought as to the best type of autonomic attack. When Dr. Zaimis and I first worked on the methonium salts, we drew attention to the differing proportionate actions which various blocking agents had on sympathetic and parasympathetic functions, with the idea that a pure sympathetic paralysis might be of especial advantage. If one examines the effects of anti-adrenalins or of reserpine, however, doubts arise as to whether this is true. There are sufficient instances in which the sympathetic and parasympathetic, as it were, hold each other in check, to suggest that some measure of parasympathetic block may be desirable if the sympathetic is also blocked. One may, perhaps, not regard it as so disappointing, after all, that *useful* selective ganglion block has not materialized.

But it also becomes clear that, if the neurogenic hypothesis is true, ganglion block is not the ideal treatment, since no one believes that the autonomic overactivity *arises* in the ganglia. The great question, indeed, is, how does it arise? Is it by changes in the baroceptor organs, or by an abnormality in the "set" of the vasomotor center, or by psychological maladjustment, or by some structural abnormality of the central autonomic pathways allowing them to reverberate, like an obsessive memory, when they should have sunk to quiescence? One can hardly talk usefully, for the simple reason of our profound ignorance, when it comes to definite and specifically located statements, about the physiology and pharmacology of central autonomic pathways. The treatment of hypertension by ganglion block is, I think, a rational one, about as rational as the use of liver extract in pernicious anemia. But it may well be that our real understanding of it must wait, like so many other problems, on advances in our knowledge of central nervous function.

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